View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Queen's University Research Portal

Beyond HIV microbicides: multipurpose prevention technology (MPT) products

Malcolm, R. K., Boyd, P., McCoy, C. F., & Murphy, D. J. (2014). Beyond HIV microbicides: multipurpose prevention technology (MPT) products. BJOG: An International Journal of Obstetrics and Gynaecology, 121(S5), 62-69. DOI: 10.1111/1471-0528.12852

Published in:
BJOG: An International Journal of Obstetrics and Gynaecology

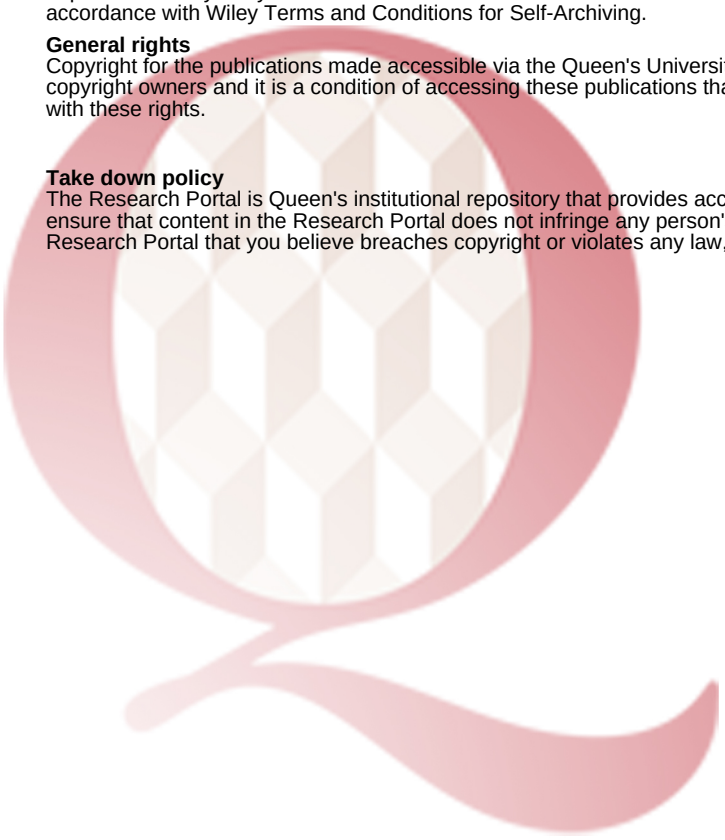
Document Version:
Peer reviewed version

Queen's University Belfast - Research Portal:
Link to publication record in Queen's University Belfast Research Portal

Publisher rights
© 2014 Royal College of Obstetricians and Gynaecologists
This is the peer reviewed version of the following article: Malcolm RK, Boyd P, McCoy CF, Murphy DJ. Beyond HIV microbicides: multipurpose prevention technology products. BJOG 2014; 121 (Suppl. 5): 62–69, which has been published in final form at http://onlinelibrary.wiley.com/doi/10.1111/1471-0528.12852/references. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Self-Archiving.

General rights
Copyright for the publications made accessible via the Queen's University Belfast Research Portal is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy
The Research Portal is Queen's institutional repository that provides access to Queen's research output. Every effort has been made to ensure that content in the Research Portal does not infringe any person's rights, or applicable UK laws. If you discover content in the Research Portal that you believe breaches copyright or violates any law, please contact openaccess@qub.ac.uk.



Download date:15. Feb. 2017

Beyond HIV microbicides: multipurpose prevention technology (MPT) products

R. Karl Malcolm*, Peter Boyd, Clare F McCoy, Diarmaid J. Murphy

School of Pharmacy, Queen's University Belfast, Belfast BT9 7BL, UK

Correspondence: Prof R Karl Malcolm, School of Pharmacy, Queen's University Belfast, Belfast BT9 7BL, UK, T: 028 9097 2319, E: k.malcolm@qub.ac.uk

Shortened running title: Beyond HIV microbicides: MPT products

Summary

Multi-purpose prevention technologies (MPTs) that aim to simultaneously prevent unintended pregnancy, human immunodeficiency virus type 1 (HIV-1) infection and other sexually transmitted infections (STIs) are among the most innovative and complex products currently in development within women's sexual and reproductive healthcare. In this review article, MPTs are placed within the wider context of combination products, combination drug products and multi-indication products. The current MPT product landscape is mapped and assessed with reference to existing products for the corresponding single indications, before identifying the gaps in the current MPT product pipeline and highlighting priority products and challenges moving forward.

Introduction

Since 2010, following the first encouraging data to emerge from clinical testing of an antiretroviral-based HIV microbicide candidate[1], there has been extensive talk, consideration and early stage development around next generation products, termed 'multipurpose prevention technologies' (MPTs), that aim to combine HIV prevention with prevention of unintended pregnancy and/or prevention/treatment of other sexually transmitted infections (STIs) and reproductive tract infections (RTIs). In addition to the significant number of agenda-setting and commentary/review articles published on MPTs,[2-10] there has also been a limited number of original research articles describing new MPT concepts.[11-15] MPTs are not a new product class, despite the new (and somewhat confusing) name. Male condoms, which offer effective barrier protection against pregnancy, HIV and other STIs, have been used for more than 400 years, and their female counterparts have been available since the 1980s. However, despite their effectiveness, condoms are often not used consistently and correctly and have clear limitations for women. Therefore, there is an urgent need for new and innovative MPT products that offer women in particular greater choice and improved acceptability in controlling their sexual and reproductive health.

With recent interest focused almost exclusively on microbicidal-based (and, more specifically, antiretroviral-based) strategies for prevention of sexual transmission of HIV, newer MPT approaches have inevitably included at least one active pharmaceutical ingredient (API), resulting in either a 'combination product' (CP) or a 'combination drug product' (CDP), to use more conventional pharmaceutical regulatory terminology (Table

1, Figure 1). For example, the microbicide-releasing diaphragm device recently reported is considered a 'combination product' (Table 1, Figure 2), comprising a medical device (a cervical barrier diaphragm) coupled with an additional drug delivery function (controlled release of an antiretroviral microbicide).[13] A vaginal ring device that provided simultaneous sustained/controlled release of an antiretroviral, a contraceptive progestogen and/or an anti-HSV drug would formally be classified as 'combination drug products' (Table 1, Figure 1, Figure 2).[16,17] Regulatory definitions of a 'medical device' and a 'drug delivery device', for which there is often considerable confusion, are also provided in Table 1.

Combination drug products: the wider context for MPTs

Many of the MPT strategies currently being pursued rely solely on simultaneous delivery of muliple APIs, and are therefore formally classified as CDPs. For this reason, it is worth considering CDPs in more detail to help contextualise MPTs. CDPs (also known as 'fixed-dose combinations'; Table 1, Figure 1, Figure 2) have become increasingly important in the public health arena. CDPs comprise a particular combination of actives, in a fixed ratio of doses, that is both safe and effective and where each API contributes to the overall therapeutic effect. For patients, these combination products often lead to simplified therapy, improved clinical effectiveness, reduced incidence of adverse side effect and increased adherence.[18-20] For pharmaceutical companies, CDPs also offer excellent opportunities for life cycle management of marketed drug products. Currently marketed CDPs are mapped in Figure 1 according to the number of APIs in the product and the number of clinical conditions that the product is intended to treat. Unlike the vast

majority of drug products that contain a single active and treat a single disease, marketed CDPs comprise two, three and even four actives for treatment of a single disease, most commonly HIV/AIDS, asthma, malaria, contraception, high blood pressure and tuberculosis (Figure 1). Examples of CDPs that are used in the treatment of two distinct (but clinically related) diseases include Caduet®/Envacar® (containing atorvastatin and amlodipine; used in the treatment of high cholesterol and high blood pressure, respectively) and Juvisync™ (containing sitagliptin and simvastatin; used in the treatment of diabetes and high cholesterol, respectively) (Figure 1). Not surprisingly, the complexities associated with preclinical and clinical development of multi-indication products, including CDPs and MPTs, are signficantly greater than those for single API products.

Multipurpose prevention technologies (MPTs)

MPTs are effectively a sub-category of CPs and CDPs, specifically focused on prevention of a triad of specific (and inter-related) clinical conditions within women's sexual and reproductive health, namely pregnancy, HIV infection and/or other STIs. As such, MPTs are multi-indication products (Figure 1), either comprising (i) multiple active agents, individually effective for a different indication, (ii) a single active agent effective for multiple indications (e.g. a single active drug with both microbicidal and contraceptive properties), or (iii) one or more active agents incorporated into a medical device (e.g. a microbicide-releasing condom or diaphragm). Figure 3 provides an overview of the formulation/dosage form options being used or actively developed for

prevention/treatment of the individual clinical indications and the various combinations of indications that define MPTs.

It is worth making several comments based on Figure 3. First, the mature contraceptive market offers the greatest choice of formulation options, with thirteen distinct product types administered across a very diverse range of delivery routes (i.e. oral, vaginal, subdermal, subcutaneous, cervical and transdermal). This diversity is rather unique, particularly given the rather limited choice of APIs currently available for contraception. The main factors contributing to the diversity of dosage forms and delivery routes used for hormonal contraceptives include: (i) contraceptive drugs may be delivered locally or systemically, although most are administered systemically, (ii) the relatively high therapeutic potency of hormonal contraceptive agents, at least compared with currently available antiretrovirals and anti-STI agents, and (iii) consequently, the need for only very low doses for clinical efficacy. It is likely that the next generation of MPT products will be based around these existing contraceptive technologies rather than a completely new product concept.

Second, seven MPT strategies have been identified within the intersection areas of the Venn diagram in Figure 3 (products identified by the following codes: 1DJ, 6G, 6+9D, 9D, 11A, 11G and 11AG). Most of these MPT products are in pre-clinical development (condoms being the exception) and all are based upon existing contraceptive technologies, most notably vaginal gels, vaginal ring and cervical diaphragms. Interestingly, this observation largely reflects current HIV microbicide development priorities and MPT product preference research, in which women rate favourably products that are easy to use and/or increase adherence.[21] Since product adherence will be

critical for the clinical effectiveness of MPTs (as it is for HIV microbicides), sustained release products, such as vaginal rings, subcutaneous injectables and subdermal implants, have been identified using target product profile (TPP) methodology as a development priority.

Third, current MPT development work is focused primarily on HIV+contraception and HIV+HSV strategies (Figure 2), the former reflecting women's health priorities in Africa[5] where HIV is most prevalent, and the latter the fact that vaginally-administered tenofovir is inherently active against both HIV and HSV.[11,14,22]

Where are the gaps in the MPT product pipeline?

It is not surprising that HIV prevention is a major component of most current MPT strategies, since MPT research has stemmed primarily from within the HIV microbicide field. Based on consideration of Figure 3 and the associated scientific literature, certain gaps and deficiencies in the MPT product landscape can be readily identified.

(i) There is an over-reliance on reverse transcriptase inhibitors (RTIs) for topical (vaginal and rectal) HIV prevention. This is particularly true of tenofovir and to a lesser extent dapivirine, both of which are lead candidate microbicides currently in late stage clinical testing. Anti-HIV compounds other than RTIs are slowly beginning to emerge as potential microbicides. These include small-molecule CCR5 entry inhibitors such as maraviroc and CMPD167,[23-26] integrase inhibitors,[27] protease inhibitors[28] and various peptides/proteins.[29,30] However, very few of these HIV inhibitor molecules have progressed to early stage clinical testing as microbicides, despite the fact that many are already marketed for HIV treatment.

(ii) There is presently a distinct lack of interest/commitment in the development of non-antiretroviral HIV prevention methods, although this has not always been the case. Previously, several non-antiretroviral microbicide candidates, including nonoxynol-9, cellulose sulphate, BufferGel, Carraguard and PRO 2000, were evaluated in late stage effectiveness trials, although none demonstrated protection.[31] Vivagel, a second generation non-antiretroviral microbicide comprising a dendrimer-based gel product, has shown a broad spectrum of activity against HIV and HSV-2,[32,33] although it is mostly being evaluated in ongoing clincial studies for the treatment of bacterial vaginosis. The general lack of specificity and potency of these non-antiretroviral microbicides is mostly attributed to the fact that their mechanisms of antiviral activity are confined to disrupting the virus or preventing its attachment to cells in the vaginal lumen rather than the intracellular activity afforded by antiretrovirals. Also, many of these non-antiretroviral microbicides were developed as coitally dependent, on-demand vaginal gel formulations, which, although being considered for MPTs, are probably not as high a priority as sustained release products.

(iii) Given ongoing concerns over the short and long term side effects associated with hormonal contraceptives (such as irregular bleeding, weight gain, nausea or lower libido, and slightly increased risk for certain cancers), the lack of innovation around non-hormonal contraceptive methods that might be leveraged by new MPT products is rather surprising. Barrier methods (exemplified by condoms, diaphragms and cervical caps) and the Paragard® intrauterine device, are the most common non-hormonal devices used for contraception. Of these products, only the diaphragm is presently being considered as a potential MPT, either used in combination with an antiretroviral gel[34] or through direct

incorporation (and subsequent slow release) of an antiretroviral drug into the polymeric spring core component of diaphragm device itself.[13] Investment in new contraceptive technologies, and particularly non-hormonal methods, is needed to achieve consistent and correct contraceptive use, to lower unintended pregnancy rates, and to widen contraceptive choice for women.

(iv) There appears to be no current activity in the development of non-HIV MPT methods (Figure 3), despite the fact that strategies that focus on preventing pregnancy and other STIs are deemed priority indications in a number of countries, including India, China and potentially Europe and the USA.[21] Potent new drugs that specifically target other STIs are generally lacking, and identifying pathogen-specific actives for both bacterial and viral STIs is certainly a key priority in future MPT development.

(v) MPT product concepts comprising a vaccine component to target any of the three clinical indications that define MPTs are much further down the developmental pipeline compared with non-biologic strategies.[10] Although HIV and contraceptive vaccines are in development, only an HPV vaccine is currently available (Figure 3). In general, biologic-based MPT product concepts remain largely unexplored. A vaccine and microbicide combination for preventing HIV-1 sexual transmission has been reported recently, albeit the components are administered separately via the intramuscular and intravaginal routes, respectively.[35] Potential MPT product concepts offering a vaccine component include a single-dose depot injection comprising a contraceptive hormone (like Depo Provera®) combined with an HIV or STI antigen, or a vaginal ring device delivering a vaccine candidate (either HIV or STI) and one or more ARV-based HIV microbicides. Vaginal

ring devices suitable for formulation and sustained release of biologics have been reported.[15,36]

(vi) Sustained/controlled release progestogen-only products in the form of subcutaneous injectables (e.g. Depo Provera) and subdermal implants (e.g. Nexplanon/Implanon) are already marketed for long-term contraception. In fact, Depo Provera is the most common form of contraception in Africa. It is conceivable that MPT products could be developed based around existing injectable and implantable progestogen formulations. However, a major challenge would be achieving sufficient loading and release of the antiretroviral and/or anti-STI drug(s) to prevent sexual transmission of the associated microorganism(s). To date, this product concept has not been widely considered.

What are the MPT product priorities moving forward?

A key consideration for future MPT products will be user adherence to the prescribed regimen, a particularly pertinent issue for on-demand products. The importance of user adherence is well understood and documented within the contraceptive field, where the differences between actual-use and perfect-use failure rates are highly dependent on whether the products are user-dependent (e.g. oral pill, diaphragm, vaginal ring) or non-user dependent (e.g. intrauterine device, injectable, implant, and sterilisation).[37,38] Growing concern over (lack of) adherence to experimental microbicide products and placebos in clinical studies, particularly with vaginally administered gel products,[1,39,40] has led to prioritisation of sustained release over on-demand methods for MPTs. Sustained drug release vaginal rings are already marketed for contraception (Nuvaring®

and Progering®), estrogen replacement therapy (Estring® and Femring®) and hormone supplementation during *in vitro* fertilisation (Fertiring®). Rings releasing small molecule antiretrovirals are also at the forefront of current HIV microbicide efforts.[41-43.] A vaginal ring comprising 25 mg of the non-nucleoside reverse transcriptase inhibitor dapivirine (also known as TMC120) dispersed within a silicone elastomer matrix[44-46] is presently being tested in two Phase III studies (MTN-020 and IPM027) in Africa. Although high levels of acceptability and user adherence have been reported for non-microbicide vaginal rings [47-57], it is not yet clear if microbicide-releasing rings will offer improved adherence. The ability to combine and/or compartmentalise multiple drugs within a single ring device bodes well for developing a practical ring-based MPT strategy.[15,23,26,41,58]

The challenges moving forward

Despite the obvious urgency for development of new MPT products for use in both developed and developing countries, the only options currently available for simultaneous protection against unintended pregnancy, HIV and/or other STIs remain male and female condoms. None of the MPTs currently in development have yet progressed beyond preclinical testing, although an investigational new drug (IND) application has recently been submitted for the tenofovir/levonorgestrel vaginal ring. When they do eventually make it to clinic, many complex hurdles and challenges will likely prevent a quick route to market. For example, the same issues that may challenge antiretroviral-based HIV prevention around the potential for development of resistant virus will also apply to MPT products containing antiretrovirals. This is likely to fuel demand for sustained release products that promote user adherence. Also, given the complexity of multi-indication

combination products having constituent parts corresponding to drug products, medical devices and biologics, MPTs will invariably involve unique and challenging regulatory considerations. Regulatory challenges, considerations, and decisions will be product-specific as well as indication-specific. In both the EU and the US, a single regulatory center will have primary jurisdiction for the MPT product, and assignment is based on the product's primary mode of action (although quite how the primary mode of action will be defined is still unclear for many product concepts). Other major challenges for MPTs include the design and assessment of results from clinical studies and appropriately scaled manufacturing solutions for what are likely to be relatively complex and possibly expensive devices.

Conclusions

Increased awareness and interest in new MPTs have largely been stimulated by recent progress in the HIV microbicide field with the continued clinical development of the tenofovir vaginal gel and the dapivirine vaginal ring. Based on the current clinical schedules, and depending upon study outcomes, successful approval of these products is unlikely before 2015. Meantime, in preparation for success and in order to ensure rapid follow-through, it is imperative that new MPT concepts are considered, funded, developed and evaluated now. Perhaps more than any other drug/combination product type to date, MPTs will require diverse and extensive collaborative efforts across multiple disciplines in order to achieve the laudable goal of creating innovative and converged technologies that simulataneously address the most important issues in women's sexual and reproductive health today.

Disclosure of interest

The authors report no conflicts of interest in the preparation of this manuscript.

Funding

No funding received.

Acknowledgements

The authors thank Bethany Young Holt and Joseph Romano for their helpful insights and comments around construction of Figure 2.

References

1 Abdool Karim Q, Abdool Karim SS, Frohlich JA, Grobler AC, Baxter C, Mansoor LE, *et al.* Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. *Science* 2010;329:1168–74.

2 Friend DR, Doncel GF. Combining prevention of HIV-1, other sexually transmitted infections and unintended pregnancies: Development of dual-protection technologies. *Antiviral Res* 2010;88:S47–54.

3 Friend DR. Intravaginal rings: controlled release systems for contraception and prevention of transmission of sexually transmitted infections. *Drug Delivery Trans Res* 2011;1:185–93.

4 Friend DR. Drug delivery in multiple indication (multipurpose) prevention technologies: systems to prevent HIV-1 transmission and unintended pregnancies or HSV-2 transmission. *Expert Opin Drug Deliv* 2012;9:417–27.

5 Harrison PF, Hemmerling A, Romano J, Whaley KJ, Young Holt B. Developing multipurpose reproductive health technologies: an integrated strategy. *AIDS Res Treat* 2013;790154.

6 Holt BY, Kilbourne-Brook M, Stone A, Harrison P, Shields WC. Multipurpose prevention technologies for sexual and reproductive health: gaining momentum and promise. *Contraception* 2010;81:177–80.

7 Malcolm RK, Fetherston SM. Delivering on MPTs: addressing the needs, rising to the challenges and making the opportunities. *Contraception* 2013;88:321–5.

8 Thurman AR, Clark MR, Doncel GF. Multipurpose prevention technologies: biomedical tools to prevent HIV-1, HSV-2, and unintended pregnancies. *Infect Dis Obstet Gynecol* 2011;2011:1–10.

9 Thurman AR, Doncel GF. Herpes simplex virus and HIV: genital infection synergy and novel approaches to dual prevention. *Int J STD AIDS* 2012;23:613–9.

10 Whaley KJ, Hanes J, Shattock R, Cone RA, Friend DR. Novel approaches to vaginal delivery and safety of microbicides: biopharmaceuticals, nanoparticles, and vaccines. *Antiviral Res* 2010;88:S55–6.

11 Andrei G, Lisco A, Vanpouille C, Introini A, Balestra E, van den Oord J, *et al*. Topical tenofovir, a microbicide effective against HIV, inhibits herpes simplex virus-2 replication. *Cell Host Microbe* 2011;10:379–89.

12 Ball C, Krogstad E, Chaowanachan T, Woodrow KA. Drug-eluting fibers for HIV-1 inhibition and contraception. *PLoS ONE* (2012);7:e49792.

13 Major I, Boyd P, Kilbourne-Brook M, Saxon G, Cohen J, Malcolm RK. A modified SILCS contraceptive diaphragm for long-term controlled release of the HIV microbicide dapivirine. *Contraception* 2013;88:58–66.

14 Mesquita PM, Rastogi R, Segarra TJ, Teller RS, Torres NM, Huber AM, *et al*. Intravaginal ring delivery of tenofovir disoproxil fumarate for prevention of HIV and herpes simplex virus infection. *J Antimicrob Chemother* 2012;67:1730–8.

15 Moss JA, Malone AM, Smith TJ, Kennedy S, Nguyen C, Vincent KL, *et al*. Pharmacokinetics of a multipurpose pod-intravaginal ring simultaneously delivering five drugs in an ovine model. *Antimicrob Agents Chemother* 2013;57:3994–7.

16 Podolsky SH, Greene JA. Combination drugs--hype, harm, and hope. *N Engl J Med* 2011;365:488–91.

17 Lodola A, Developing Combination Drugs in Preclinical Studies, pp 3-16, in Drug Safety Evaluation: Methods and Protocols, Methods in Molecular Biology, vol. 691, Jean-Charles Gautier (ed.).

18 Bangalore S, Kamalakkannan G, Parkar S, Messerli FH. Fixed-dose combinations improve medication compliance: a meta-analysis. *Am J Med* 2007;120:713–9.

19 Pan F, Chernew ME, Fendrick AM. Impact of Fixed-Dose Combination Drugs on Adherence to Prescription Medications, *J Gen Intern Med* 2008;23:611–4.

20 Wertheimer AI. The economics of polypharmacology: fixed dose combinations and drug cocktails. *Curr Med Chem* 2013;20:1635–8.

21 Coalition Advancing Multipurpose Innovations (CAMI), “Multipurpose Prevention Technologies for Reproductive Health: Product Prioritization Stakeholder Meeting”, 2012, http://www.cami-health.org/documents/2012SAWG-Report-FinalReport.pdf

22 Vibholm L, Reinert LS, Søgaard OS, Paludan SR, Østergaard L, Tolstrup M, *et al*. Antiviral and immunological effects of tenofovir microbicide in vaginal herpes simplex virus 2 infection. *AIDS Res Hum Retroviruses* 2012;28:1404–11.

23 Fetherston SM, Boyd P, McCoy CF, McBride MC, Edwards KL, Ampofo S, *et al*. A silicone elastomer vaginal ring for HIV prevention containing two microbicides with different mechanisms of action. *Eur J Pharm Sci* 2012;48:406–15.

24 Forbes CJ, Lowry D, Geer L, Veazey RS, Shattock RJ, Klasse PJ, *et al*. Non-aqueous silicone elastomer gels as a vaginal microbicide delivery system for the HIV-1 entry inhibitor maraviroc. *J Control Release* 2011;156:161–9.

25 Malcolm RK, Veazey RS, Geer L, Lowry D, Fetherston SM, Murphy DJ. Sustained release of the CCR5 inhibitors CMPD167 and maraviroc from vaginal rings in rhesus macaques. *Antimicrob Agents Chemother* 2012;56:2251–8.

26 Malcolm RK, Forbes CJ, Geer L, Veazey RS, Goldman L, Klasse PJ, *et al*. Pharmacokinetics and efficacy of a vaginally administered maraviroc gel in rhesus macaques. *J Antimicrob Chemother* 2013;68:678–83.

27 Terrazas-Aranda K, Van Herrewege Y, Hazuda D, Lewi P, Costi R, Di Santo R, *et al*. Human immunodeficiency virus type 1 (HIV-1) integration: a potential target for microbicides to prevent cell-free or cell-associated HIV-1 infection. *Antimicrob Agents Chemother* 2008;52:2544–54.

28 Herrera C, Shattock RJ. Potential use of protease inhibitors as vaginal and colorectal microbicides. *Curr HIV Res* 2012;10:42–52.

29 Dereuddre-Bosquet N, Morellato-Castillo L, Brouwers J, Augustijns P, Bouchemal K, Ponchel G, *et al*. MiniCD4 microbicide prevents HIV infection of human mucosal explants and vaginal transmission of SHIV162P3 in cynomolgus macaques, *PLoS Pathog* 2012;8:e10030.

30 Recum HA, Pokorski JK. Peptide and protein-based inhibitors of HIV-1 co-receptors. *Exp Biol Med* 2013;238:442–9.

31 Vanpouille C, Arakelyan A, Margolis L. Microbicides: still a long road to success. *Trends Microbiol* 2012;20:369–75.

32 Rupp R, Rosenthal SL, Stanberry LR. 2007. VivaGel (SPL7013 Gel): a candidate dendrimer-microbicide for the prevention of HIV and HSV infection. *Int J Nanomedicine* 2007;2:561–66.

33 Price CF, Tyssen D, Sonza S, Davie A, Evans S, Lewis GR, *et al*. SPL7013 gel (VivaGel®) retains potent HIV-1 and HSV-2 inhibitory activity following vaginal administration in mumans. *PLoS One* 2011;6: e24095.

34 Frezieres RG, Walsh T, Kilbourne-Brook M, Coffey PS. Couples' acceptability of the SILCS diaphragm for microbicide delivery. *Contraception* 2012;85:99–107.

35 Barouch DH, Klasse PJ, Dufour J, Veazey RS, Moore JP. Macaque studies of vaccine and microbicide combinations for preventing HIV-1 sexual transmission. *Proc Natl Acad Sci USA* 2012;109:8694–8.

36 Morrow RJ, Woolfson AD, Donnelly L, Curran R, Andrews G, Katinger D, Malcolm RK. Sustained release of proteins from a modified vaginal ring device. *Eur J Pharm Biopharm* 2011;77:3–10.

37 Winner B, Peipert JF, Zhao Q, Buckel C, Madden T, Allsworth JE, *et al*. Effectiveness of long-acting reversible contraception, *New Engl J Med* 2012; 366:1998–2007.

38 Efficacy of contraceptive methods: A review of the literature. *Eur J Contracept Reprod Health Care* 2010;15:4–16.

39 Ferrer RA, Morrow KM, Fisher WA, Fisher JD. Toward an information–motivation–behavioral skills model of microbicide adherence in clinical trials, *AIDS Care* 2010;22:997–1005.

40 Tolley EE, Harrison PF, Goetghebeur E, Morrow K, Pool R, Taylor D, et al. Adherence and its measurement in phase 2/3 microbicide trials. *AIDS Behav* 2010;14:1124–36.

41 Kiser PF, Johnson TJ, Clark JT. State of the art in intravaginal ring technology for topical prophylaxis of HIV infection. *AIDS Rev* 2012;14:62–77.

42 Malcolm RK, Fetherston SM, McCoy CF, Boyd P, Major I. Vaginal rings for delivery of HIV microbicides. Int J Women's Health 2012;4:595–605.

43 Friend DR, Kiser PF. Assessment of topical microbicides to prevent HIV-1 transmission: Concepts, testing, lessons learned. *Antiviral Res* 2013;99:391–400.

44 Malcolm RK, Woolfson AD, Toner CF, Morrow RJ, McCullagh SD. Long-term, controlled release of the HIV microbicide TMC120 from silicone elastomer vaginal rings. *J Antimicrob Chemother* 2005;56:954–6.

45 Woolfson AD, Malcolm RK, Morrow RJ, Toner CF, McCullagh SD. Intravaginal ring delivery of the reverse transcriptase inhibitor TMC 120 as an HIV microbicide. *Int J Pharm* 2006;325:82–9.

46 Nel A, Smythe S, Young K, Malcolm K, McCoy C, Rosenberg Z, Romano J. Safety and pharmacokinetics of dapivirine delivery from matrix and reservoir intravaginal rings to HIV-negative women. *J Acquir Immune Defic Syndr* 2009;51:416–23.

47 Gilliam M, Holmquist S, Berlin A. Factors associated with willingness to use the contraceptive vaginal ring. Contraception. 2007 Jul;76(1):30–4.

48 Hardy E, Hebling EM, Sousa MH, Almeida AF, Amaral E. Delivery of microbicides to the vagina: difficulties reported with the use of three devices, adherence to use and preferences. Contraception. 2007 Aug;76(2):126–31.

49 Weisberg E, Fraser IS, Lacarra M, Mishell DR, Jackanicz T. Effect of different insertion regimens on side effects with a combination contraceptive vaginal ring. Contraception. 1997 Oct;56(4):233–9.

50 Montgomery ET, van der Straten A, Cheng H, Wegner L, Masenga G, von Mollendorf C, et al. Vaginal ring adherence in sub-Saharan Africa: expulsion, removal, and perfect use. AIDS Behav. 2012 Oct;16(7):1787–98.

51 Szarewski A. High acceptability and satisfaction with NuvaRing use. Eur J Contracept Reprod Health Care. 2002 Dec;7 Suppl 2:31–6; discussion 37–9.

52 Stewart FH, Brown BA, Raine TR, Weitz TA, Harper CC. Adolescent and young women's experience with the vaginal ring and oral contraceptive pills. J Pediatr Adolesc Gynecol. 2007 Dec;20(6):345–51.

53 Speroff L. Efficacy and tolerability of a novel estradiol vaginal ring for relief of menopausal symptoms. Obstet Gynecol. 2003 Oct;102(4):823–34.

54 Roumen FJ, Apter D, Mulders TM, Dieben TO. Efficacy, tolerability and acceptability of a novel contraceptive vaginal ring releasing etonogestrel and ethinyl oestradiol. Hum Reprod. 2001 Mar;16(3):469–75.

55 Dieben TOM, Roumen FJME, Apter D. Efficacy, cycle control, and user acceptability of a novel combined contraceptive vaginal ring. Obstet Gynecol. 2002 Sep;100(3):585–93.

56 Roumen FJ, Dieben TO. Clinical acceptability of an ethylene-vinyl-acetate nonmedicated vaginal ring. Contraception. 1999 Jan;59(1):59–62.

57 Buckler H, Al-Azzawi F. The effect of a novel vaginal ring delivering oestradiol acetate on climacteric symptoms in postmenopausal women. BJOG. 2003 Aug;110(8):753–9.

58 Johnson TJ, Gupta KM, Fabian J, Albright TH, Kiser PF. Segmented polyurethane intravaginal rings for the sustained combined delivery of antiretroviral agents dapivirine and tenofovir. *Eur J Pharm Sci* 2010;39:203–12.

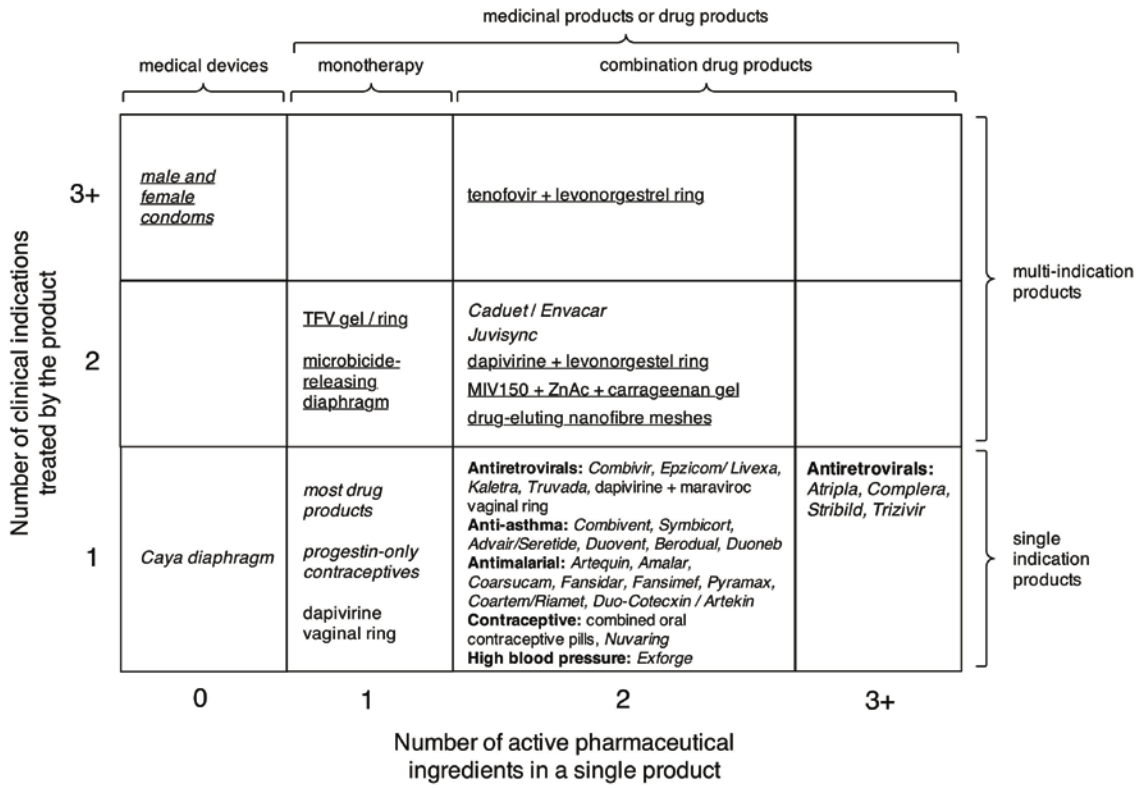


Figure 1. Mapping of number of active pharmaceutical ingredients per product versus number of clinical indications per product for ‘combination products’ and ‘combination drug products’ (including MPTs) (see Table 1 for definitions). MPTs fall within the product categories targeting two or more clinical indications, irrespective of the number of pharmaceutical ingredients in the product. Italicised text indicates representative marketed products or product classes. Non-italicised text indicates products in development. Underlined text represents MPT products.

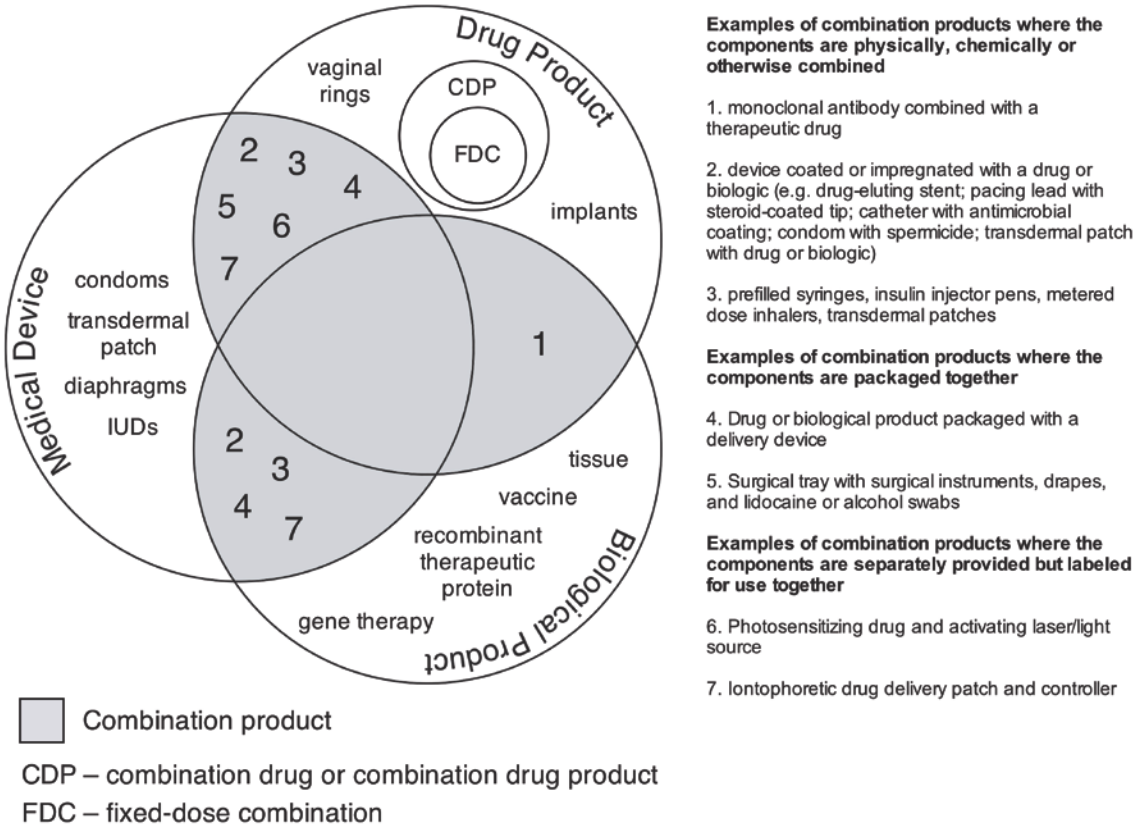


Figure 2. Classification and regulatory framework for drug products, biologic products, medical devices and their combination products (depicted in grey). MPTs may be placed within several of these sub-categories, including medical devices, combination products, and combination drug products (CDP). A combination biological product (not shown) targeted at two or more clinical indications (pregnancy, HIV and/or other STIs) would also classify as a MPT product. The product types indicated in the diagram are examples representative of the classification.

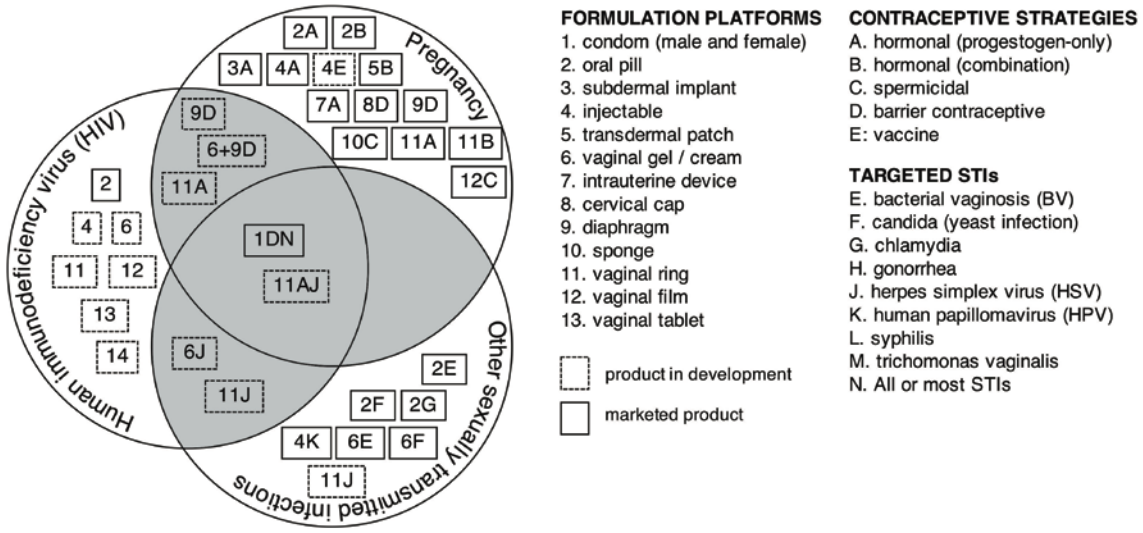


Figure 3. Marketed and development product landscape for prevention/treatment of HIV, pregnancy, and other sexually transmitted diseases. All of the products captured within the HIV circle contain one or more antiretroviral compounds that act against HIV. Intersection areas (depicted in grey) represent MPT products. * HPV can infect areas that are not covered by a condom, and therefore condoms may not fully protect against HPV (http://www.cdc.gov/std/hpv/stdfact-hpv.htm)

Table 1. Definition of key terms

Term	Definition
'combination drug', 'combination drug product' or 'fixed dose combination'	a single dosage form comprising two or more active pharmaceutical ingredients (APIs); may target single or multiple (often related) disease states; in tablet or capsule form, combination drugs are referred to as 'polypill' or 'combopill'
'combination product'	a product comprised of any combination of a drug and a device; a biological product and a device; a drug and a biological product; or a drug, device, and a biological product
'combination therapy', 'polytherapy' or 'polypharmacy'	use of more than one medication or therapy; most commonly used to treat a single disease; may involve administration of separate drug products or combination drug products; conditions treated with combination therapy include tuberculosis, leprosy, cancer, malaria, and HIV/AIDS; 'polypharmacy' is often defined as the use of five or more regular medications (more common in older patients).
'drug delivery device'	any device that provides delivery of one of more drug substances
'medical device'	"any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of: diagnosis, prevention, monitoring, treatment or alleviation of disease; diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap; investigation, replacement or modification of the anatomy or of a physiological process; control of conception; and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means;" (Medical Devices Directive 93/42/EEC (MDD))
'medicinal product'	"any substance or combination of substances presented as having properties for treating or preventing disease in human beings; [or] any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis." (European Union Directive 2004/27/EC)
'monotherapy'	use of a single medication for treatment of a single disease
'multi-purpose prevention technology'	the term is exclusively used to describe technologies, preferably single-product technologies, that simultaneously address at least two of the following clinical needs: (i) prevention of unintended pregnancy, (ii) prevention of HIV, (iii) prevention or treatment of other sexually transmitted or reproductive tract infections